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Review

Minocycline, focus on mechanisms of resistance, antibacterial activity, and clinical effectiveness: Back to the future

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ABSTRACT

Objectives: The increasing crisis regarding multidrug-resistant (MDR) and extensively drug-resistant microorganisms leads to appealing therapeutic options.
Methods: During the last 30 years, minocycline, a wide-spectrum antimicrobial agent, has been effective against MDR Gram-positive and Gram-negative bacterial infections. As with other tetracyclines, the mechanism of action of minocycline involves attaching to the bacterial 30S ribosomal subunit and preventing protein synthesis.
Results: This antimicrobial agent has been approved for the treatment of acne vulgaris, some sexually transmitted diseases and rheumatoid arthritis. Although many reports have been published, there remains limited information regarding the prevalence, mechanism of resistance and clinical effectiveness of minocycline.
Conclusion: Thus, we summarize here the currently available data concerning pharmacokinetics and pharmacodynamics, mechanism of action and resistance, antibacterial activity and clinical effectiveness of minocycline.

Contents

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1. Introduction

Minocycline is a highly lipophilic molecule, second-generation and semisynthetic tetracycline analogue [1]. It can effectively cross the blood–brain barrier and impedes various Gram-positive and Gram-negative bacteria [2]. It was first introduced in the 1960s. Its primary mechanism of action for antimicrobial activity is based on the fact that tetracyclines attach to the bacterial 30S ribosomal subunit and prevent protein synthesis [3]. Minocycline has more tissue absorption into the cerebrospinal fluid and the central nervous system (CNS) and a longer half-life in comparison with first-generation tetracyclines [2]. Modification in ring D through carbons 7–9 is the basis for the higher efficacy of minocycline [4]. It has been mainly approved and used for the treatment of some sexually transmitted diseases and rheumatoid arthritis by the US Food and Drug Administration (FDA) [5,6]. When minocycline is orally administered, there is quick and excellent absorption and tissue penetration, longer half-life and potent bioavailability; thus, it has a superior pharmacokinetic profile compared with first-generation tetracyclines [7–10]. Currently, most reports have focused on the non-antibiotic properties of minocycline. We summarize the currently available data concerning pharmacokinetics and pharmacodynamics, mechanism of action and resistance, antibacterial activity and clinical effectiveness of minocycline.

2. Structural characterization

Minocycline (7-dimethylamino-6-dimethyl-6-deoxytetracycline) is named chemically as (4*S*,4a*S*,5a*R*,12a*R*)-4,7-bis(dimethylamino)-1,10,11,12*a*-tetrahydroxy-3,12-dioxo-4*a*,5,5*a*,6-tetrahydro-4*H*-tetracene-2-carboxamide [11]. Its chemical formula is C23H27N3O7 and its molecular weight is 457.5 g/mol. Minocycline is a tetracycline containing a dimethylamino group at position 7 without methyl and hydroxy groups at position 5; therefore, it shows more lipophilicity than other tetracyclines, with optimal tissue penetration [9,12,13]. Fig. 1 shows the chemical structure of minocycline and other tetracyclines.

3. Pharmacokinetics and pharmacodynamics

Preliminary studies of intravenous (i.v.) minocycline pharmacokinetics have showed a desired serum concentration (C_{max} = 3–8.75 mg/mL) compared with other tetracyclines. Minocycline is mainly expelled via the faeces and at a low rate via the urine (5–12%) [14]. Minocycline is metabolized by the liver [9,12]. The excretion half-life of minocycline ranges from 15 to 23 h, which is the same as doxycycline, but significantly longer than that of the first tetracycline [15]. However, similar to tetracycline, minocycline's protein-binding capacity is 76% [9]. Minocycline's circulation volume ranges from 67.5 to 115 L [9,12]. The tissue to plasma ratio in the liver, gallbladder and bile fluids, prostate and genitourinary organs is >1.0. In addition, the tissue serum concentration ratio is 3.80 in the lung [9]. Human and animal model studies have demonstrated that the cerebrospinal fluid (CSF) penetration of minocycline is insignificant (>50% of serum concentrations) [7,8,12,16,17]. Kidney failure and liver cirrhosis have a slight effect on the half-life and area under the concentration-time curve (AUC) of minocycline, however, careful administration is recommended for these patients [9,18]. The oral administration of minocycline has a more suitable pharmacokinetic profile than the earliest tetracycline [19].

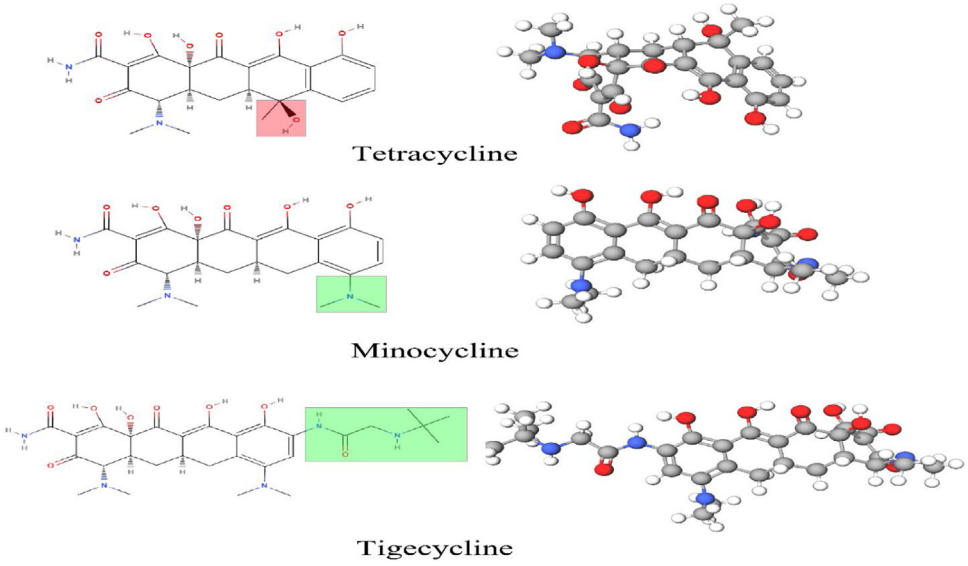

Fig. 1. The chemical structure of minocycline and other tetracyclines.

4. Adverse effects

It has been indicated that minocycline has side effects in patients [20]. Frequent minocycline adverse effects include gastrointestinal symptoms (e.g. nausea, diarrhoea, flatulence, vomiting), vestibular disturbance (dizziness) and cutaneous symptoms (e.g. hyperpigmentation of skin and mucous membranes, pruritis, urticaria and photosensitive rash) [20,21]. Appropriate clinical monitoring is recommended for long-term treatment with minocycline [22]. Hyperpigmentation is a frequent adverse effect in patients on long-term minocycline therapy in a range of organs, including the skin, teeth, bone, thyroid and sclera [20,21,23–28]. However, the hyperpigmentation process is reversible; the nature of minocycline-induced cutaneous hyperpigmentation is mostly cosmetic and not associated with adverse clinical effects [25,29]. The proposed predisposing factors for hyperpigmentation, still uncertain, in patients include higher doses [20] and aging [30]. However, in most cases, the hyperpigmentation process is reversible, and the pigmentation fades after minocycline cessation [31]. In a systematic review [32] on the adverse effects of doxycycline and minocycline, no divergence was shown in gastrointestinal complaints. Minocycline had a larger adverse effect of CNS symptoms, such as vertigo. For the most part, three serious but infrequent side effects include dose-related toxicity reactions with early onset resulting in single-organ dysfunction, hypersensitivity syndrome (pneumonitis, eosinophilia, hepatitis, pancreatitis, nephritis and serum sickness-like syndrome), and autoimmune disorders (drug-induced lupus erythematosus-like eruption, autoimmune hepatitis and polyarteritis nodosa) [21,33]. Another serious minocycline-related side effect is anaphylaxis (a life-threatening reaction to drugs) that was reported in a 56-year-old woman after receiving oral minocycline [21]. Vasculitis neuropathy following exposure to minocycline has also been reported [34]. A Cochrane review has proposed that it should no longer be used as first-line therapy, partly owing to the indefinite risk of adverse effects [33,35,36].

5. Characteristics of minocycline

5.1. Mechanism of action

The main mechanism of action in minocycline is similar to the other tetracycline drug family [37]. Tigecycline acts as an inhibitor of bacterial protein translation (elongation of the peptide chain) via binding reversibly to a helical region (H34) on the 30S subunit of bacterial ribosomes; this blocks the incorporation of amino acid residues into the elongating peptide chains, resulting in the loss of peptide formation and bacterial growth [10,37] (Fig. 2).

5.2. Mechanisms of resistance

A variety of mechanisms, including the efflux pump and modification or protection of the antibiotic target sites are involved in resistance to tetracyclines. The *tet* efflux genes code for membrane-related proteins that flow tetracyclines out of bacteria, and lead to minimum inhibitory concentration (MIC) reduction of the drug intracellularly, consequently protecting the ribosomes. The Tet proteins, such as Tet(B), Tet(A), tet(K), Tet(M), and Tet(S), have the potential to reduce the susceptibility or resistance to minocycline [38–41]. The tet(B) efflux pump, associated with the major facilitator superfamily, and most commonly spread, is found in Gram-negative pathogens and confers resistance to tetracycline, doxycycline and minocycline [39,42–44]. Nevertheless, the expression of *tetB* in *tetB*-positive, tetracycline-resistant multidrug resistant (MDR) *Acinetobacter baumannii* strains has been shown to reduce susceptibility notably or elevate the MICs of minocycline (from <1 to 8 μg/mL) in European hospitals [45].

Another efflux mechanism, including resistance-nodulation-division (RND)-type efflux pumps (e.g. AdeFGH, AdeIJK) has also been proposed for minocycline resistance [43]. Moreover, there is a direct link between the lack of *tetB* gene and minocycline susceptibility [42]. In an experimental study, it was found that 93.3% (154/165) of *A. baumannii* strains were resistant to minocycline and harboured the *tetB* gene [46]. Thus, it was

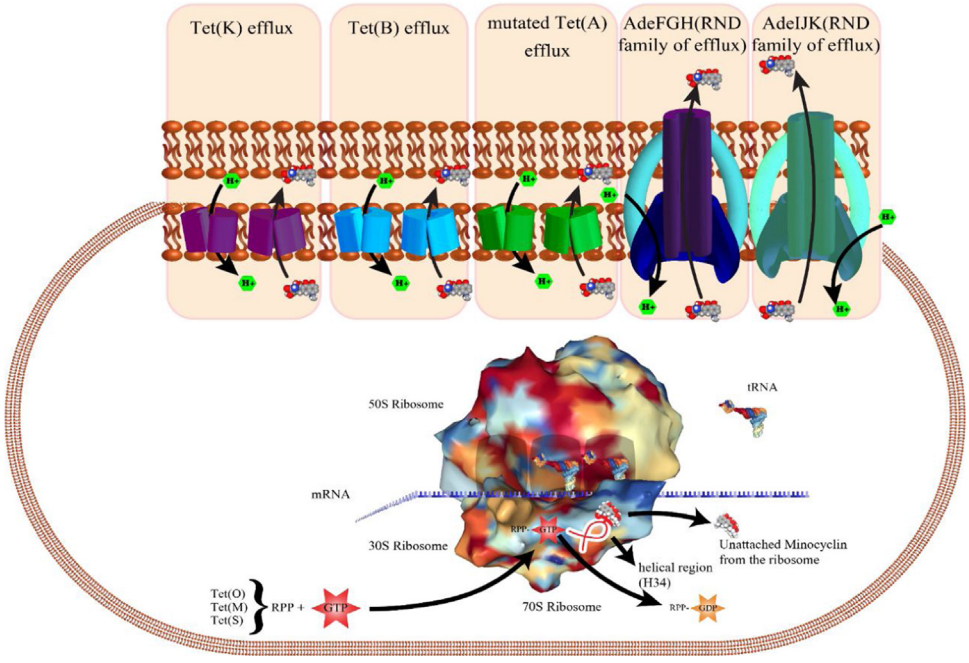

Fig. 2. Minocycline mechanism of action and resistance.

proposed that the *TetB* serves as a possible target for rapid diagnostic gene testing to define minocycline resistance [46]. Alterations in the interdomain loop region of the *tetA*(A) tetracycline resistance gene enhance minocycline efflux [47].

Minocycline resistance of the methicillin-resistant *Staphylococcus pseudintermedius,* which harbours *tet(M)* and confers resistance to all three tetracyclines, has been found [42]. The *tet* genes encoding ribosomal protection proteins (RPPs) confer a wide spectrum of antibiotic resistance. The RPPs are cytoplasmic proteins with GTPase activity, resulting in resistance to both doxycycline and minocycline [39,48]. A conformational alteration occurs when the antibiotic molecule attaches to the ribosome. A Tet(O) protein binds to guanosine-5′-triphosphate (GTP) to form a Tet(O)-GTP complex. Then, this complex attaches to the ribosome and continue the antibiotic molecule away. The GTP molecule is then cleaved to form a Tet(O)–guanosine diphosphate (GDP) complex; finally, this complex is unattached from the ribosome, allowing it to return to its standard conformation. On the other hand, it is believed that the energy from the GTP hydrolysis unbinds the antibiotic from the ribosome, and the antibiotic remains unaffected [39,49,50].

The *tetM* gene has been found in *A. baumannii* and encodes an RPP from tetracycline, doxycycline and minocycline. This gene is a homologue of the *Staphylococcus aureus* gene; a genetic horizontal transfer between bacteria has been proposed [51]. The RPPs are found in various spectra of bacteria such as Gram-positive, anaerobic and nonenteric Gram-negative pathogens. Efflux genes are extensively disseminated and are usually associated with large plasmids, which frequently harbour other antibiotic resistance genes [39,52]. Minocycline resistance through *tet(S)*, encoded by a new, small, low copy number plasmid, has also been found in a human-derived oral *Streptococcus infantis* isolate [40]. Previous studies have demonstrated the presence of plasmid-located *tet(S)* in *Lactobacillus plantarum* CCUG 43738, which proves that lactobacilli from various sources can harbour acquired antibiotic resistances [53–56]. The *L. plantarum* CCUG 43738 strain shows an

Table 1
International minocycline in vitro susceptibility breakpoints.

Bacterial family, species	International breakpoints standard	Broth microdilution (mg/L)	Disk diffusion (mm)
Enterobacteriaceae	EUCAST	–	–
	FDA	–	–
	BSAC	–	–
	CLSI	S ≤ 4, R ≥ 16	S ≥ 16, R ≤ 12
Acinetobacter spp.	EUCAST	–	–
	FDA	–	–
	BSAC	–	–
	CLSI	S ≤ 4, R ≥ 16	S ≥ 16, R ≤ 12
Staphylococcus spp.	EUCAST	S ≤ 0. 5, R > 1	S ≥ 23, R < 20
	FDA	–	–
	BSAC	S ≤ 0.5, R > 1	S ≥ 28, R ≤ 27
	CLSI	S ≤ 4, R ≥ 16	S ≥ 19, R ≤ 14
Enterococcus spp.	EUCAST	–	–
	FDA	–	–
	BSAC	–	–
	CLSI	S ≤ 4, R ≥ 16	S ≥ 19, R ≤ 14
Streptococcus groups A, B, C and G	EUCAST	S ≤ 0. 5, R > 1	S ≥ 23, R < 20
	FDA	–	–
	BSAC	–	–
	CLSI	–	–
S. pneumoniae	EUCAST	S ≤ 0. 5, R > 1	S ≥ 24, R < 21
	FDA	–	–
	BSAC	–	–
	CLSI	–	–
Haemophilus influenzae	EUCAST	S ≤ 1, R > 2	S ≥ 24, R < 21
	FDA	–	–
	BSAC	–	–
	CLSI	–	–
Moraxella catarrhalis	EUCAST	S ≤ 1, R > 2	S ≥ 25, R < 22
	FDA	–	–
	BSAC	–	–
	CLSI	–	–
Pseudomonas spp.	EUCAST	–	–
	FDA	–	–
	BSAC	–	–
	CLSI	–	S ≥ 19, R ≤ 14
Neisseria meningitidis	EUCAST	S ≤ 1, R > 2	–
	FDA	–	–
	BSAC	–	–
	CLSI	S ≤ 2	S ≥ 26
Burkholderia cepacia complex	EUCAST	–	–
	FDA	–	–
	BSAC	–	–
	CLSI	S ≤ 4, R ≥ 16	S ≥ 19, R ≤ 14
Stenotrophomonas maltophilia	EUCAST	–	–
	FDA	–	–
	BSAC	–	–
	CLSI	S ≤ 4, R ≥ 16	S ≥ 19, R ≤ 14

BSAC, British Society for Antimicrobial Chemotherapy; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; R, resistance; S, sensitive.

unusual phenotypic resistance to minocycline (MIC = 256 μg/mL), and it has been found to harbour a *tet(S)* gene found on a plasmid of ~14 kb [53]. Vilacoba et al. detected the presence of *tet(B)* located on an insertion sequence of an ISCR2 mobile element in all minocycline-resistant *A. baumannii* isolates. This genetic platform of the *tet(B)* gene confirms a novel mechanism that makes it possible to spread among *A. baumannii* isolates [57]. Fig. 2 depicts the minocycline mechanism of resistance.

6. International in vitro susceptibility breakpoints

Currently, several laboratory methods, including broth microdilution and disk diffusion, have been introduced for the determination of in vitro susceptibility to tigecycline. Bacteria that are susceptible to tetracycline are also considered to be susceptible to doxycycline and minocycline [58,59]. However, some bacteria defined as intermediate or resistant to tetracycline might be susceptible to doxycycline, minocycline or both according to the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [58,59]. Because CLSI criteria used to evaluate tigecycline susceptibility were not available, the tigecycline international in vitro susceptibility breakpoints in bacteria according to EUCAST, CLSI [58,59], the FDA [60] and the British Society for Antimicrobial Chemotherapy (BSAC) [61] are shown in Table 1.

7. Antibacterial activity

The drugs available to treat MDR *A. baumannii* are limited, so i.v. minocycline is a new and valuable repurposing of an old antibiotic for the intensive treatment of *Acinetobacter* spp. and other Gram-positive and Gram-negative pathogens. Minocycline is used for the treatment of a wide range of diseases, such as acne vulgaris, skin and soft tissue infections (e.g. *Staphylococcus aureus*, *Actinomyces* spp.), Lyme disease, gastrointestinal infections (e.g. *Vibrio cholera*, *Campylobacter* spp.), sexually transmitted diseases (e.g. *Ureaplasma urealyticum*, *Chlamydia trachomatis*, *Klebsiella granulomatis*), rickettsial infections (e.g. rickettsial pox, Rocky Mountain spotted fever), and zoonotic infections (e.g. *Brucella* spp., *Yersinia pestis*, *Chlamydia psittaci, Bartonella bacilliformis, Francisella tularensis*) [62].

The prevalence of resistance varies across different regions. For example, in the United States, minocycline resistance is low in the New England and South Atlantic regions but is high in the Middle Atlantic and East North Central regions. Tetracycline-resistant strains show varying degrees of resistance to minocycline and doxycycline. Minocycline has a low MIC_{90} at present. Obviously, the more this drug is prescribed, the greater the chance of developing resistance [63].

7.1. Minocycline resistance in A. baumannii

The use of minocycline in the treatment of MDR Gram-negative bacterial infections has been increasing. Many studies have focused on the *A. baumannii* infections. For the MDR *A. baumannii* organism (MDRO), minocycline is the second most active agent in vitro and might be the only therapeutic option in certain cases. Minocycline could also be used to treat other MDRO Gram-negative infections [64,65]. The Tigecycline Evaluation and Surveillance Trial (TEST) study reported the highest global minocycline susceptibility rate (84.5%) between 2004 and 2013 [13]. However, there are no randomized controlled experiments, and in vivo data are limited. Otherwise, minocycline has consistently shown favourable results for oral and intravenous treatment. In a systematic review of clinical evidence by Fragkou et al. [66], the role of minocycline was highlighted in the treatment of nosocomial infections caused by MDR, extensively drug-resistant (XDR) and pandrug-resistant *A. baumannii*. A favourable clinical and microbiological success rate of minocycline activity was shown in *A. baumannii* isolates.

The role of oral minocycline in the treatment of wound infections was found by Griffith et al. [67]; seven of eight cases with MDR *A. baumannii* soft tissue infections were clinically treated 4–6 weeks after the use of minocycline alone or in combination with another antibiotic

In Argentina, Vilacoba et al. have reported that the emergence of minocycline resistance in *A. baumannii* reaches 40% of isolates in different centres [68] and, in Iran, 17% of *A. baumannii* hospital isolates exhibited resistance to minocycline [69]. The *tet(A)* is the bacterial tetracycline resistance gene and generally confers resistance to tetracycline alone, whereas *tet(B)* confers resistance to tetracycline and minocycline [45]; therefore, if an organism has an elevated MIC to tetracycline, the *tetA* or *tetB* genes do not necessarily cause resistance to minocycline. In the study conducted by Lomovskaya et al. in 2018, 258 *A. baumannii* strains were used to define MIC frequency dispensations for the *tetB*-positive and *tetB*-negative sets of strains. Among them, 93 *tetB*-negative strains showed a minocycline MIC $\leq$ 4 μg/mL. Among 165 *tetB*-positive strains, 154 had a minocycline MIC > 4 μg/mL [70].

In *A. baumannii*, efflux pumps are effective for transporting out tetracycline and doxycycline. Lomoskaya et al. [70] confirmed that only 11 of 165 isolates (6.7%) were TetB-positive and susceptible to minocycline, whereas 93 of 93 strains were minocycline-susceptible and TetB-negative. Therefore, the presence of TetB can be an important reason for sensitivity to minocycline [46]. It is noteworthy that sensitivity to minocycline is not associated with the presence of the RND pumps, so tigecycline-resistant *A. baumannii* can remain susceptible to minocycline [37].

Carbapenems have been identified as suitable agents for the treatment of MDR *A. baumannii* infections but carbapenem-resistant *A. baumannii* (CRAB) has rapidly increased in frequency. CRAB accounts for 65% of *A. baumannii* pneumonia cases in Europe and the United States, whereas more than 60% of isolates in Asia have been found to be both pandrug and carbapenem-resistant [71]. Minocycline can overcome many mechanisms of tigecycline resistance in *A. baumannii*. Furthermore, minocycline has favourable pharmacokinetic and pharmacodynamic properties, and excellent in vitro activity against drug-resistant *A. baumannii*. The Eurofins Surveillance Network reported that resistance to minocycline decreased from 56.5% in 2003–2005 to 30.5% in 2009–2012 [72].

7.2. Minocycline resistance in Enterobacteriaceae

Minocycline susceptibility in carbapenemase-producing carbapenem-resistant Enterobacteriaceae such as *Escherichia coli* (48.5%) and *Klebsiella pneumoniae* (3.3%) were reported by Yamamoto in 2017 [73]. The level of resistance to minocycline in Gram-negative pathogens varies from 4.2% for *A. baumannii* to 30.3% for extended-spectrum β-lactamase (ESBL)–positive *K. pneumoniae*. In ESBL-positive isolates of *E. coli*, *K. pneumoniae* and *Klebsiella oxytoca,* resistance to minocycline is at least twofold higher in comparison with all isolates of each species. For example, minocycline-resistant *E. coli* isolates are 11.2%, and 25.1% of ESBL-positive isolates of *E. coli* exhibit resistance to minocycline. Minocycline-resistance is common in Gram-negative pathogens, but rates of cross-resistance to tigecycline are typically very low, ranging from 0.01% for *E. coli* to 1% in *Enterobacter cloacae* [74].

Cha from South Korea indicated that among 85 salmonella strains, 67 strains were resistant to nalidixic acid, and 41 strains were resistant to sulfisoxazole. Additionally, 31 and 30 strains were

resistant to cefazolin and minocycline, respectively [75]. EUCAST does not set breakpoints for Enterobacteriaceae, and there are limited data on the use of minocycline in Enterobacteriaceae. The TEST study reported that 71.4% of *K. pneumoniae* isolates are globally susceptible to minocycline, but this rate decreases to 52.2% in isolates resistant to carbapenems. It is worthy of note that the susceptibility of *K. pneumoniae* to minocycline has gradually declined between 2004 and 2011, but then a 22.9% increase in minocycline susceptibility occurred between 2011 and 2013 [76]. According to the study of DiPersio et al., 85% of MDR *Serratia marcescens* (N = 20) were resistant to minocycline. MDR *E. cloacae* (N = 126) resistance rates against minocycline were the highest (81.0%), and 75% of MDR *Enterobacter aerogenes* (N = 24) were minocycline-resistant [77].

Bartha has shown that the presence of tetX in *E. coli* dramatically increases the MIC values of different tetracycline derivatives, including minocycline [78]. In Gram-negative bacteria, resistance to tetracycline, doxycycline and minocycline is conferred by the *tet(B)* gene. RPPs displace tetracycline from the 30S ribosomal subunit via GTP, depending on attachment to the ribosomal binding site. In the study by Zeng et al., the *U. urealyticum* and *Mycoplasma hominis* displayed low resistance rates to josamycin, doxycycline and minocycline (<10%) in both symptomatic and asymptomatic groups [79]. Horiki et al. evaluated resistance of *Helicobacter pylori* to minocycline. They found that resistance to minocycline was quite as low as amoxicillin (0.06%). Minocycline could constitute the next candidate drug for third-line therapy in Japan [80].

7.3. Minocycline resistance in Gram-positive bacteria

Minocycline-resistance in Gram-positive pathogens has a difference in range, from 0.6% for *S. aureus* to 22.5% for *Enterococcus faecalis*. Minocycline resistance is slightly higher in isolates of methicillin-resistant *S. aureus* (MRSA; 1.3%). *Stenotrophomonas maltophilia* is naturally resistant to carbapenems, thus, the optimal treatment for *S. maltophilia* infection in clinical practice is usually minocycline, cotrimoxazole, levofloxacin or combination therapy [81]. Ullah [82] indicated that 60 of 130 clinical isolates of *S. aureus* were MRSA, whereas 70 isolates (54.0%) were methicillin-susceptible *S. aureus* (MSSA). Seventy-four strains (56.9%) were resistant to tetracycline (TET-R), 30 strains (23.1%) were resistant to minocycline and 23 strains (17.7%) were resistant to doxycycline [82].

Antibiotic resistance is a global problem in regard to *Propionibacterium*. Generally, there is high-level resistance to trimethoprim–sulfamethoxazole (TMP-SMX), clindamycin and macrolides, whereas resistance to tetracyclines and levofloxacin has a low potential. Minocycline is reliably effective when doxycycline or TMP-SMX fails to treat uncomplicated cutaneous abscesses due to community-associated MRSA [83]. A single G-C transition mutation in 16S rRNA of the small ribosomal subunit in *Propionibacterium acnes* is associated with minocycline resistance. There is also an association between resistance to tetracycline and doxycycline. Luk [84] indicated that 47 strains (54.7%) of the 86 *P. acnes* were found to be resistant to at least one antibiotic. Eighteen (20.9%), 14 (16.3%), 14 (16.3%), 46 (53.5%) and 14 (16.3%) of strains were resistant to erythromycin, tetracycline, doxycycline, clindamycin and minocycline, respectively [84,85]. One criterion to explain the link between antibiotic resistance and response is based on the type of antibiotic used, topical or systemic. The MICs of resistant strains are 2–16 mg/L for minocycline and 4–64 mg/L for tetracycline, thereby overlapping with plasma levels. Hence, the concentration in the follicles might be sufficient to inhibit the resistant strains. Although minocycline has the highest lipophilicity among other cyclines, the partition in the skin sebum seems to be insufficient to inhibit some resistant isolates [86]. Low-dose administration of IR tetracyclines, such as lymecycline 150 mg/daily or minocycline 50 mg/daily, is not subtherapeutic and can increase the risk of resistance [87]. In Gram-positive cocci, efflux proteins confer resistance to tetracyclines, but not minocycline [16]. The initial reports of resistance originate from the United States, with one of the highest minocycline MICs reported (8–16 mg/mL); however, there are little data available [88].

In acne treatment, the highest resistance to minocycline is observed respectively in Hong Kong, Singapore, Egypt, India and Colombia [89]. In a study by Boswihi et al., 143 group B streptococcus (GBS) isolates, collected from mothers in Kuwait, were resistant to minocycline (89.5%) [90]. The minocycline-resistant isolates contained *tetM* (94.5%), *tetL* (1.6%), *tetO* (3.9%) and *tetK* (0.8%) [90]. Ciric et al. showed that minocycline resistance is encoded by *tet(S)* on a novel small, low copy number plasmid in an oral *S. infantis* isolate [40].

The *tet(K)* gene protects bacteria from tetracycline by a resistance mechanism known as tetracycline efflux. This mechanism prevents the accumulation of tetracycline in the bacterial cell [91]. According to Huys et al., high-level resistance to both minocycline and tetracycline suggests the involvement of an acquired ribosomal protection mechanism [91]. In Gram-positive bacteria, *tet* genes *tet(M)*, *tet(O)*, *tet(Q)*, *tet(S)* and *tet(W)* are the most commonly detected ribosomal protection. It has been determined that tetracycline resistance in *L. plantarum* has so far been associated with the presence of only the *tet(M)* gene [56].

Minocycline monotherapy should be avoided to prevent the development of resistant strains. Furthermore, cross-resistance or cross-susceptibility is found in a limited number of isolates, indicating that tetracycline should not be used as a predictive determinant for susceptibility or resistance to minocycline. Susceptibility to minocycline should be assessed routinely by the laboratory according to CLSI criteria. Moreover, the use of minocycline alone or in combination needs to be guided by the results of clinical trials and further laboratory studies [92].

7.4. Minocycline activity in combination with other drugs

In recent years, the use of minocycline with other compounds and its beneficial effects have been considered in various studies. MDR *A. baumannii* is currently a major cause of respiratory infections in intensive care unit patients [93]. Combination therapy with minocycline, tigecycline, polymyxins, carbapenems and daptomycin is a common treatment strategy for MDR *A. baumannii* [94]. The results of these studies show that polymyxin B would break apart the cell membrane, exert a suitable functioning of the efflux pumps and thereby enhance the activity of minocycline [95]. One study mentioned mortality in the range of 30.8–58.3% in *A. baumannii* bacteraemia. This rate is dependent on the antimicrobial combination used [96]. In the study by Bowers et al., minocycline and polymyxin B were checked out for pandrug-resistant *A. baumannii*, and they found that the MIC of each drug decreased with the combination of polymyxin B and minocycline [97]. Research studies have indicated that combinations such as colistin–minocycline, colistin–rifampicin and colistin–meropenem are synergistic against XDR *A. baumannii* strains in vitro. When colistin is unavailable, the minocycline–meropenem combination might be an alternative option for the treatment of infections caused by XDR *A. baumannii* [98].

Periodontitis (gum disease) is an infectious disease that damages the soft tissue and destroys the bone that supports teeth; periodontitis leads to tooth loss. Minocycline is widely used for the treatment of periodontitis [99]. Minocycline promotes periodontal tissue regeneration and has a wide antibacterial spectrum. The combination of minocycline and metronidazole can

synergistically contribute to the reconstruction of periodontal tissues, enhance the antibacterial effect and reduce the level of cytokines in gingival crevicular fluid in the process of periodontitis treatment [100].

Acne vulgaris is a common chronic skin disease involving blockage and/or inflammation of pilosebaceous units [101]. Minocycline is an effective treatment for moderate to moderately severe inflammatory acne vulgaris. Compared with minocycline alone, the combination of photodynamic therapy (PDT) with minocycline significantly improves clinical efficacy in patients with moderate to severe facial acne [102].

Combination therapy can be used for the treatment of antifungal-resistant fungi. Fluconazole with minocycline can work synergistically against fluconazole-resistant *Candida albicans*. Their mechanism of action suggests that minocycline causes fluconazole to penetrate the biofilm better and leads to intracellular calcium release instead of affecting the uptake and efflux of fluconazole [103]. *Klebsiella pneumoniae* carbapenamase (KPC)-producing *K. pneumoniae* is not only resistant to β-lactams, but also shows reduced susceptibility to other antimicrobial classes especially used in clinical practice. Studies have shown that the combination of minocycline with aminoglycoside exerts a strong synergistic and bactericidal impact in susceptible isolates for infections caused by KPC-producing *K. pneumonia* and can effectively prevent the emergence of resistant mutants [104]. KPC-producing *K. pneumoniae* usually causes serious infections in immunocompromised patients, so the treatment should be timely and efficacious [104]. Worldwide reports of minocycline resistance rates in different pathogens are shown in Table 2.

8. Minocycline effectiveness in clinical trials

Minocycline is an effective antibiotic against various infections of the skin (especially severe acne), urinary and respiratory tracts, and genital system (gonorrhoea, syphilis, chlamydia, mycoplasma). It is also used as a second-line drug in infections in patients with a penicillin treatment allergy. Owing to the side effects following the systemic administration of minocycline, its use in such infections has been limited and is now more common for the treatment of acne vulgaris. Recently, many studies have focused on the interesting anti-inflammatory and neuroprotective efficacy of minocycline, a topic that was first mentioned in 2007 in case reports [3]. In this review, we surveyed 40 clinical trials that investigated the effect of minocycline on various diseases. About one-third of the studies (13 cases) were conducted in the United States. India and Canada had five investigations. Iran, Japan and Brazil each has three studies, ranked in third position among others.

Several studies have investigated the effect of minocycline on schizophrenia. Wehring et al. surveyed the effect of adjunctive minocycline to clozapine (an antipsychotic drug) in patients with schizophrenia in 2018 [105]. After 10 weeks of treatment, it was found that the administration of minocycline could increase the clozapine plasma level and be effective in those with schizophrenia. In another study, the beneficial effect of minocycline on negative symptoms such as social withdrawal, emotional blunting and apathy, which are unaffected by common antipsychotic drugs in early schizophrenia, was investigated. The authors studied the efficacy of minocycline treatment for 1 year in early psychosis to improve negative symptoms in 144 participants compared with placebo given in Brazil and Pakistan. It was found that minocycline could mainly reduce negative symptoms in the early course of the schizophrenia [106].

Many studies have investigated the effect of minocycline on various mental disorders, including depression. Savitz et al., in 2018, showed that treatment of bipolar depression with adjuvant therapy of minocycline and aspirin might be an efficacious strategy [107]. Ruiz-Antoran et al., in 2018, evaluated the effectiveness of

Table 2
Prevalence of minocycline resistance worldwide.

Study, year	Location	Method	Bacteria	No. of isolates	Resistant (%)	MIC_{50}/MIC_{90} (μg/mL)
Luk et al. (2013) [84]	Hong Kong	AD	*Propionibacterium acnes*	47	16.3	1
Tan et al. (2007) [134]	Singapore	MBD	*P. acnes*	44	11.5	0.5–6
Moon et al. (2012) [135]	Korea	DD	*P. acnes*	100	10	–
Mendoza et al. (2013) [136]	Colombia	AD	*P. acnes*	100	1	4
Sardana et al. (2015) [89]	India	AD	*P. acnes*	52	1.9	8
Ross et al. (2001) [137]	USA	AD	*P. acnes*	73	4	0.5–4
Luk et al. (2013) [84]	Hong Kong	AD	*P. acnes*	47	16.3	1
Gonzalez et al. (2010) [138]	USA	Etest	*P. acnes*	49	0	MIC_{50} = 0.5MIC_{90} = 2
Nakase et al. (2014) [139]	Japan	AD	*P. acnes*	69	0	MIC_{90} = 0.5
Ishida et al. (2008) [140]	Japan	AD	*P. acnes*	48	0	MIC_{90} = 0.5
Mendoza et al. (2013) [136]	Tokyo	AD	*P. acnes*	69	0	MIC_{90} = 0.5
Song et al. (2011) [141]	Korea	Etest	*P. acnes*	31		MIC_{50} = 0.065MIC_{90} = 0.125
Ullah et al. (2012) [82]	Pakistan	AD	*Staphylococcus aureus*	130	23.08	MIC_{50} = 2MIC_{90} = 64
Ullah et al. (2012) [82]	Pakistan	AD	MRSA	60	50	MIC_{50} = 8MIC_{90} = 64
Vilacoba et al. (2015) [68]	Argentina	DD	*Acinetobacter baumannii*	77	40	–
Mohajeri et al. (2013) [69]	Iran	DD	*A. baumannii*	104	16.3	–
Lomovskaya et al. (2018) [70]	United States	MBD	*A. baumannii*	258	59.6	MICs > 4
Cha et al. (2013) [75]	South Korea	DD	*Salmonella*	85	35.2	–
DiPersio et al. (2007) [77]	United States	MBD	Multidrug-resistant *K. pneumoniae*	174	0 to 70	MIC_{50} = 4MIC_{90} = 32
Wang et al. (2014) [142]	China	DD	*U. urealyticum* *M. hominis*	1889 45	10 10	–
Horiki et al. (2009) [80]	Japan	DD	*H. pylori*	3521	0.06	–

AD, agar dilution; BMD, broth microdilution; DD, disk diffusion; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug-resistant; MRSA, methicillin-resistant *S. aureus*; NA, not available.

Table 3
Data from clinical trials of minocycline against various diseases.

Study (year)	Dosage, mg/day, route	Duration	Country	Disease	No. of patients	Outcome
Cha et al. (2019) [143]	–/local	6 months	South Korea	Peri-implantitis	50	Local delivery of minocycline combined with surgical treatment provides significant benefits in terms of clinical parameters and radiographic bone fill, with a higher treatment success rate in the short healing period
Hokari et al. (2018) [144]	Minocycline ointment	4 weeks	Japan	Chronic periodontitis	30	Although local administration of minocycline may slightly help improve clinical, microbiological and crevicular cytokine levels in periodontal pockets, a PDT did not show any effects
Abbas et al. (2016) [117]	Minocycline ointment	6 months	India	Generalized chronic periodontitis	60	Significant reduction in clinical parameters with improvement in periodontal status on application of minocycline ointment, as an adjunct to periodontal flap surgery, in generalized chronic periodontitis
Arruda et al. (2018) [115]	Triple antibiotic solution (minocycline, metronidazole, ciprofloxacin), 1 mg/mL	1 week	Brazil	Apical periodontitis	48	Significantly improved root canal disinfection; effects were at least comparable with calcium hydroxide–chlorhexidine paste
Chiappe et al. (2015) [116]	Minocycline microgranules; each microgranule contains 0.35 mg	3 months	Argentina	Chronic periodontitis	26 nonsmoker volunteers	Minocycline microgranules adjunct to scaling and root planning resulted in greater reduction of BOP and PD, higher CAL gain, increased probability of Pg suppression and retarded recolonization of Td than root instrumentation alone
Williams et al. (2001) [145]	Local	9 months	United States	Periodontitis	748	SRP plus minocycline more effective than SRP alone
Ho et al. (2011) [119]	100 mg of minocycline taken orally twice daily	8 weeks	United States	HIV	7	No discernible effects of minocycline on CSF, blood HIV-1 RNA, or biomarkers of immune activation and inflammation; this pilot study of biological responses to minocycline suggests little potential for its use as an adjunctive antiviral or immunomodulating therapy in chronic untreated HIV infection.
Emadi-Kouchak et al. (2015) [118]	100 mg twice daily	6 weeks	Iran	HIV	46 HIV patients	Significantly greater and more rapid improvement in depressive symptoms of HIV-AIDS patients receiving 100 mg minocycline twice daily compared with placebo
Nakasujja et al. (2013) [120]	100 mg of minocycline or matching placebo orally every 12 h	24 weeks	United States	HIV	73 participants	Minocycline was safe and well tolerated in HIV-positive individuals; however, it did not improve HIV-associated cognitive impairment
Sacktor et al. (2011) [121]	100 mg or matching placebo orally every 12 h	24 weeks	United States	HIV-associated cognitive impairment	107	Minocycline was safe and well tolerated in individuals with HIV-associated cognitive impairment, but cognitive improvement was not observed
Cukras et al. (2012) [112]	100 mg twice daily	6 months	United States	Diabetic macular oedema	5	Minocycline as primary treatment was associated with improved visual function, central macular oedema and vascular leakage, comparing favourably with historical controls from previous studies
Syngle et al. (2014) [113]	100 mg	6 weeks	India	Type 2 diabetes mellitus (T2DM)	50	6-week oral treatment with minocycline was safe, well tolerated and significantly improved peripheral and autonomic neuropathy in type 2 diabetic patients
Lin et al. (2012) [114]	Subgingival minocycline administration	6 months	Taiwan	Type 2 diabetes mellitus (T2DM)	28	Nonsurgical periodontal therapy with or without subgingival minocycline application may achieve significant periodontal improvement and moderate improvement in HbA1c, but had no significant effect on plasma levels of IL-6, CRP, or sRAGE in patients with poorly controlled T2DM. For patients with both periodontal disease and diabetes, nonsurgical periodontal treatments might be helpful in diabetic control
Gold et al. (2019) [130]	Topical minocycline	12 weeks	USA	Acne vulgaris	961	Significantly reduced both inflammatory and noninflammatory lesions in patients with moderate to severe acne
Dreno et al. (2001) [131]	100 mg minocycline	Over 3 months	France	Acne vulgaris	332	Minocycline and zinc gluconate are both effective in the treatment of inflammatory acne, but minocycline has a superior effect, evaluated as 17% in our study

Table 3 (*Continued*)

Study (year)	Dosage, mg/day, route	Duration	Country	Disease	No. of patients	Outcome
Wehring et al. (2018) [105]	50-mg capsule twice daily for 1 week, increased to 100 mg capsule twice daily for the remainder of the study	10 weeks	USA	Schizophrenia	52	Increase in clozapine plasma levels after the initiation of minocycline compared with the placebo group
Chaudhry et al. (2012) [106]	–	12 months	Brazil and Pakistan	Schizophrenia	144 (94 completed)	The addition of minocycline to TAU early in the course of schizophrenia predominantly improves negative symptoms
Huntington Study Group DOMINO Investigators (2010) [111]	200 mg/day	—	United States	Huntington disease (HD)	114	25% improvement in TFC. The results suggest that minocycline treatment is helpful
Amiri-Nikpour et al. (2015) [127]	200 mg of oral minocycline	5 days	Iran	Ischaemic stroke	60	Patients with ischaemic stroke who received oral minocycline daily for 5 days had significantly better neurological outcomes on day 90 than controls
Srivastava et al. (2012) [146]	Oral minocycline 200 mg/day	5 days	India	Acute ischaemic stroke	50	Patients with acute ischaemic stroke had significantly better outcome with minocycline treatment compared with those given placebo; minocycline could be helpful in reducing the clinical deficits after acute ischaemic stroke
Gunn et al. (2019) [147]	200 mg/day	6–7 weeks	United States	Head and neck cancer	20	AUC comparisons for several individual symptoms and symptom interference favoured minocycline but were not statistically significant; The greatest numerical differences occurred for systemic symptoms, larger towards treatment end, and in early post-RT recovery
Metz et al. (2017) [123]	100 mg of minocycline administered orally twice daily	24 months	Canada	Multiple sclerosis	142	The risk of conversion from a clinically isolated syndrome to multiple sclerosis was significantly lower with minocycline than with placebo over 6 months but not over 24 months.
Leigh et al. (2013) [125]	Patients weighing up to 25 kg, 25 mg once daily; those weighing between 25 and 45 kg, 50 mg once daily; those weighing >45 kg, 100 mg once daily	3 months	United States	Fragile X syndrome (FXS)	55	Minocycline treatment for 3 months in children with FXS resulted in greater global improvement than placebo; treatment for 3 months appears safe, however, longer trials are indicated to further assess benefits, side effects, and factors associated with a clinical response to minocycline
Paribello et al. (2010) [124]	100 or 200 mg of minocycline daily, oral	8 weeks	Canada	FXS	20	Minocycline provides significant functional benefits to FXS patients and it is well tolerated
Kumar et al. (2016) [110]	Nasogastric, oral minocycline	3 months	India	Acute encephalitis syndrome	281	A trend towards better outcomes was observed with minocycline, especially in patients who survived the initial day in hospital
Grieco et al. (2014) [109]	3 mg/kg daily	8 weeks	USA	Angelman syndrome (AS)	25	Clinical and neuropsychological measures suggested that minocycline was well tolerated and caused improvements in the adaptive behaviours of this sample of children with AS
Ruiz-Antoran et al. (2018) [108]	3 mg/kg/day, twice daily orally	16 weeks	Spain	AS	32	Minocycline treatment for up to 16 weeks in children and young adults with AS resulted in lack of significant improvements in development indices compared with placebo treatment; treatment with minocycline appeared safe and well tolerated
Savitz et al. (2018) [107]	100 mg bid	6 weeks	United States	Bipolar depression	99	Aspirin and minocycline might be efficacious adjunctive treatments for bipolar depression
Dean et al. (2017) [148]	200 mg/day	12 weeks	Australia	Major depressive disorder	71 adults	The primary outcome was not significant, but improvements in other comprehensive clinical measures suggested that minocycline might be a useful adjunct to improve global experience, functioning and quality of life in people with major depressive disorder
Golestaneh et al. (2015) [149]	Minocycline capsules, 200 mg initially, then 100 mg every 12 h until surgery, or placebo.	—	Iran	Acute kidney injury (AKI) after cardiac surgery	38	Minocycline did not protect against AKI post-CABG

Table 3 (*Continued*)

Study (year)	Dosage, mg/day, route	Duration	Country	Disease	No. of patients	Outcome
Casha et al. (2012) [129]	Minocycline 200 mg i.v. twice daily	7 days	Canada	Spinal cord injury	52	Functional outcomes exhibited differences that lacked statistical significance but that might be suggestive of improvement in patients receiving the study drug. The minocycline regimen established in this study proved feasible and safe and was associated with a tendency towards improvement across several outcome measures
Vanelderen et al. (2015) [150]	Minocycline 100 mg once daily	14 days	Belgium	Neuropathic lumbar radicular pain	60	Not likely to be clinically meaningful
Fouda et al. (2017) [151]	400 mg minocycline i.v., followed by 400 mg minocycline oral daily	4 days	Canada	Acute cerebral haemorrhage	16	In intracerebral haemorrhage, a 400-mg dose of minocycline was safe and achieved neuroprotective serum concentrations
Narang et al. (2017) [122]	Minocycline 100 mg/day	3 months	India	Leprosy patients with recent-onset clinical nerve function impairment (NFI)	11	No serious adverse effects due to minocycline were observed; demonstrated the efficacy and safety of minocycline in recent-onset NFI in leprosy patients
Campos et al. (2011) [126]	Minocycline with EDTA solution (CATH-SAFE®, 3 mg/mL of minocycline and 30 mg/mL of EDTA)	90 days	Brazil	Catheter-related bacteraemia	204 incident catheters	Catheter-related bacteraemia-free survival was significantly higher in the minocycline-EDTA group than in the heparin group ($P = 0.005$); in conclusion, a minocycline-EDTA catheter lock solution was effective in the prevention of catheter-related bacteraemia in haemodialysis patients
Fraenkel et al. (2006) [132]	Coat		Australia	Catheter-related infection	22-bed adult general intensive care unit 646 CVCs inserted over the study period	The silver-platinum-carbon (SPC) catheter was a clinically effective antimicrobial catheter; however, the rifampicin-minocycline (RM) catheter had a lower colonization rate: SPC-impregnated catheters with RM-coated catheters. Both catheter types had low rates of catheter-related bloodstream infection.
Abla et al. (2011) [133]		3 months	United States	External ventricular drains (EVDs)	129 patients	The use of antibiotic-impregnated catheters was associated with extremely low risk of CSF infection compared to the reported mean of nearly 9% for standard EVD catheters. Infection rates for both C/R and M/R EVD catheters were 0. These results support the use of antibiotic-impregnated EVD catheters in routine clinical practice—minocycline-rifampin impregnated (M/R) ventricular catheter or a clindamycin-rifampin-impregnated (C/R)
Ishiguro et al. (2017) [152]	2–4 mg/kg/day for 2–4 days		Japan	Macrolide-resistant *Mycoplasma pneumoniae* (MRMP)	50	Minocycline showed good in vitro activity against MRMP and shortened the duration of fever in paediatric patients infected with MRMP compared with the duration of fever in patients treated with macrolides
Kawai et al. (2013) [128]	4 mg/kg twice daily	14 days	Japan	*M. pneumoniae* pneumonia (MRM)	188 children	Clinical and bacteriological efficacy of macrolides against MRM was low Minocycline rather than tosufloxacin could be considered the first-choice drug for treatment of MRM in children > 8 years of age
Pardo et al. (2013) [153]	Minocycline, 1.4 mg/kg	6 months	United States	Autism	11 children	Minocycline might have effects in the CNS by modulating the production of neurotrophic growth factors. However, in this small group of children, no clinical improvements were observed during or after the 6 months of minocycline administration

AUC, area under the curve; BOP, bleeding on probing; CAL, clinical attachment level; CRP, C-reactive protein; CSF, cerebrospinal fluid; HbA1c, haemoglobin A1c; IL-6, interleukin 6; PD, pocket depth; PDT, photodynamic therapy; Pg, *Porphyromonas gingivalis*; sRAGE, Soluble receptor for AGE; SRP, scaling and root planing; TAU, treatment as usual; Td, *Treponema denticola*; TFC, Functional capacity.

minocycline in the treatment of patients with Angelman syndrome (AS) [108]. Although minocycline treatment for AS patients did not result in significant improvements, treatment with this antibiotic seemed to be safe and well tolerated. Grieco et al. in 2014 found that minocycline in children with AS was well tolerated and caused improvements in their adaptive behaviours. They also suggested that further investigation of its optimal dosage and efficacy of long-term use in AS patients was warranted [109].

Minocycline's efficacy was also investigated in acute encephalitis syndrome, in which a trend towards better outcomes of treatment with minocycline was observed, especially in patients who survived the initial stay in hospital [110]. Moreover, the role of

minocycline in patients with Huntington disease (HD), a fatal neurotic disorder, has been studied. This study was the first trial in HD patients suggesting that minocycline treatment is not futile. Minocycline is a tetracycline that inhibits the release of apoptogenic and reactive microgliosis, important factors in the induction of HD. Minocycline slows the functional decline in HD patients by at least 25%, and this finding was accepted (P = 0.12) [111].

Some trials have focused on the effectiveness of minocycline in diabetic patients. For example, in one study, oral minocycline improved visual function, central macular oedema and vascular leakage in patients with diabetic macular oedema (DME) compared with controls [112]. Syngle et al., in 2014, indicated that the oral administration of minocycline for 6 weeks was safe and significantly improved peripheral and autonomic neuropathy in type 2 diabetic patients [113]. In a randomized controlled clinical trial by Lin et al. in 2012, it was revealed that minocycline treatment might be helpful in diabetic control for patients with both periodontal disease and diabetes [114].

Some clinical trials have investigated the efficacy of minocycline in periodontitis. Minocycline in a triple antibiotic solution significantly improved root canal disinfection compared with calcium hydroxide with chlorhexidine in patients with apical periodontitis, such as calcium hydroxide–chlorhexidine paste. Because of the easy delivery and efficacy of minocycline solution, it can be used as an appropriate disinfecting medicament for conventional non-surgical endodontic problems [115]. In a randomized clinical and microbiological trial performed by Chiappe et al., minocycline microgranules were subgingivally applied to subjects with chronic periodontitis [116]. This study showed that minocycline microgranules as an adjunct to scaling and root planing resulted in a greater reduction of bleeding on probing (BOP) and pocket depth (PD), higher clinical attachment level (CAL) gain, increased probability of *Porphyromonas gingivalis* (Pg) suppression and retarded recolonization of *Treponema denticola* (Td) than root instrumentation alone [116].

Minocycline has also been used as an ointment in the treatment of generalized chronic periodontitis and has shown significant reduction in various parameters such as gingival bleeding index, probing PD and gain in CAL in comparison with the control group. This ointment has also significantly reduced the plaque index and clinical parameters when used as an adjunct treatment to periodontal flap surgery in generalized chronic periodontitis [117].

There are several clinical trials investigating minocycline's effect on human immunodeficiency virus (HIV) infection and its complications. In one study, the antidepressant effect of minocycline was investigated in 46 HIV patients who suffered mild to moderate depression. They observed that the administration of 100 mg minocycline orally twice a day was safe and effective in improving depressive symptoms [118]. In a study by Ho et al., although minocycline was not able to modulate the HIV infection of CSF or immune activation in chronic untreated HIV-1 infection, it might have the potential to be used as an adjunctive antiviral or immunomodulating therapy in patients with chronic HIV infection [119]. In two other trials, it has been observed that despite not improving HIV-associated cognitive impairment by minocycline treatment, it was safe and well tolerated [120,121].

A few studies have surveyed the effect of minocycline on other diseases. In one study, minocycline was used in patients with recent-onset leprosy and clinical nerve function impairment (NFI). This study demonstrated minocycline treatment as an effective and safe approach in patients, without causing any serious adverse effect [122].

Minocycline has even been tested for the treatment of multiple sclerosis. Metz et al., demonstrated that minocycline reduced the risk of conversion from a first demyelinating event (clinically isolated syndrome) to multiple sclerosis compared with placebo treatment over 6 months [123].

Paribello et al. launched a trial on the treatment of fragile X syndrome (FXS, a genetic disorder that causes learning disabilities and cognitive impairment) by minocycline. This study showed that minocycline was well tolerated, providing significant functional benefits in FXS patients [124]. In another similar study in 2013, Leigh et al. surveyed the efficacy of minocycline in the treatment of FXS children and adolescents for 3 months. The results proved the safety of minocycline treatment for FXS, and this antibiotic could help relieve FXS. However, the researchers declared that longer trials were needed to assess the benefits, side effects and other aspects of this therapy further [125].

In another interesting study, minocycline was used in combination with EDTA solution to prevent bacteraemia in haemodialysis patients. This mixed solution significantly helped prevent catheter-related bacteraemia in patients (P = 0.005) [126]. Oral minocycline as an adjunct to aspirin administered daily in patients with ischaemic stroke for 5 days had significantly better neurological outcomes on day 90 than in controls [127]. One of the newer antibacterial effects of minocycline was surveyed against macrolide-resistant *Mycoplasma pneumoniae* in paediatric patients [128]. Results indicated that minocycline, rather than ofloxacin, could be considered as the first-choice drug for the treatment *of M. pneumoniae* in children older than 8 years [128]. Cash et al. in 2012 used minocycline for the treatment of acute spinal cord injury. Their trial proved minocycline treatment as safe and feasible, and they declared that it could even improve several outcome measures in acute spinal cord injury patients (but not significantly) [129].

Acne vulgaris is one of the most important diseases to be treated by minocycline, and many trials have reported the beneficial effects of this antibiotic in this regard [130,131]. In some studies, minocycline has been used in catheters. Result of these studies show that minocycline is capable of being one of the most efficacious materials used as an antimicrobial agent in catheters [126,132,133]. Table 3 depicts the clinical trials of minocycline against various diseases.

9. Conclusions

Minocycline is a wide-spectrum antibiotic and is active against MDR Gram-positive and Gram-negative bacterial infections. Minocycline's mechanism of action is to bind to the bacterial 30S ribosomal subunit and inhibit protein synthesis, as do other tetracyclines. Owing to the side effects following the systemic administration of minocycline, its use in such bacterial infections has been limited. It has been approved for the treatment of acne vulgaris, some sexually transmitted diseases and rheumatoid arthritis. However, there are limited data regarding the prevalence, mechanism of resistance and clinical effectiveness of minocycline.

Author contributions

Arezoo Asadi, Milad Abdi, Pegah Panahi, Mohammad Sholeh, Mehrdad Gholami, and Alireza Ahmadi contributed to the conception, design and drafting of the work. Ebrahim Kouhsari, Nourkhoda Sadeghifard and Abbas Maleki contributed in revising and giving final approval to the version to be published.

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